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论文

叶酸靶向的PGA联合*N*-苯乙酰化阿霉素的抗肿瘤活性

张奇;项光亚;龙娜;林佳亮;曾凡波

华中科技大学 同济医学院 药学院， 湖北 武汉 430030

摘要：

目的考察叶酸靶向的青霉素酰化酶G(PGA)联合前药*N*-苯乙酰化阿霉素(DOXP)对叶酸受体阳性肿瘤细胞的活性。方法通过双功能偶联剂EDC将叶酸与PGA偶联，荧光显微镜观察HeLa和SKOV3细胞对叶酸-PGA的摄取，MTT法检测DOXP联合叶酸-PGA对HeLa和SKOV3细胞的毒性。结果叶酸-PGA能被HeLa和SKOV3细胞选择性摄取；DOXP在叶酸-PGA的作用下对HeLa和SKOV3细胞的IC_{50}分别为0.72和0.75 μmol·L^{-1}，均低于阿霉素。结论叶酸-PGA的特异性靶向作用提高了阿霉素对HeLa和SKOV3细胞的敏感性。

关键词： 叶酸靶向 青霉素酰化酶G 阿霉素 抗肿瘤活性

Anticancer activity of *N*-(phenylacetyl) doxorubicin combined with folate-targeted PGA

ZHANG Qi; XIANG Guang-ya ; LONG Na; LIN Jia-liang; ZENG Fan-bo

Abstract:

AimTo demonstrate the specific killing of folate receptor (FR)-positive tumor cells can be achieved by folate-targeted penicillin-G amidase (PGA) combined with its prodrug substrate *N*-(phenylacetyl) doxorubicin (DOXP). MethodsFolic acid was covalently linked to PGA and folate content value was determined by quantitative UV spectrophotometry. The ability of folate conjugated PGA to hydrolyze DOXP was measured by RP-HPLC. Visual demonstration of uptake by FR(+) HeLa and SKOV3 cells was detected by using FITC labeled folate-PGA and a fluorescence microscopy. The cytotoxicity of DOXP towards the cells in the presence or absence of folate-PGA was assayed by using MTT method. ResultsThe folate-PGA has a specific activity of 29.8 U·mg^{-1}(protein). FR selectivity was confirmed by fluorescence microscopy. The combination of DOXP prodrug with folate-PGA generated higher cytotoxicity towards the FR(+) cells than free doxorubicin. The $IC_{50}$was 0.72 μmol·L^{-1} for HeLa cells and 0.75 μmol·L^{-1} for SKOV3 cells, respectively. Further, the enhanced cytotoxicity reduced greatly with the addition of free folic acid. ConclusionFolate conjugated PGA did not significantly compromise PGA catalytic activity and enabled binding prodrug-activating enzyme PGA to folate receptor expressing cells, and increased the sensitivity of the cells to doxorubicin followed by administration of its prodrug substrate.

Keywords: penicillin-G amidase doxorubicin antitumor activity folate-targeted

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作者简介:

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